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(54) Title: CANCER MANAGEMENT WITH TAMOXIFEN AND GAMMALINOLENIC ACID

(57) Abstract

Tamoxifen and gammalinolenic acid giving strong synergistic action in cancer management and preparation of medicaments therefor.

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CANCER MANAGEMENT WITH TAMOXIFEN AND GAMMALINOLENIC ACID

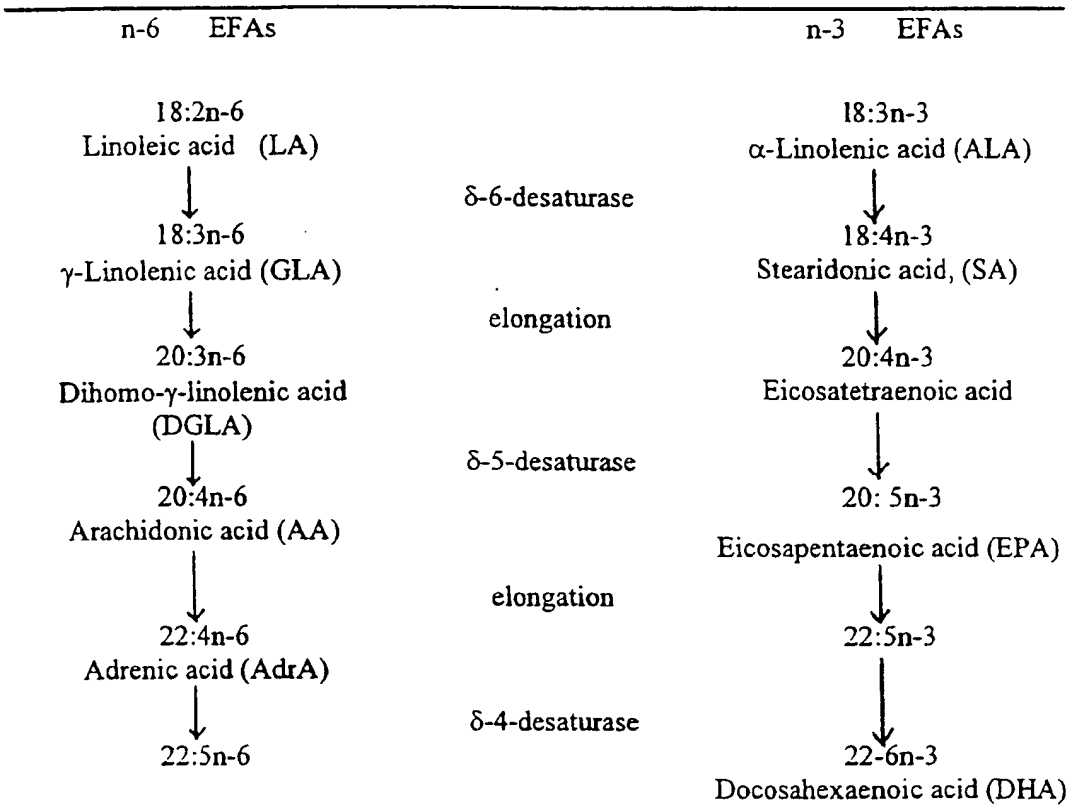
FIELD OF INVENTION

The invention relates to cancer management.

FATTY ACIDS

Certain selected unsaturated fatty acids, notably gamma-linolenic acid (GLA, 18:3n-6), dihomogammalinolenic acid (DGLA, 20:4n-6), and eicosapentaenoic acid (EPA, 20:5n-3) have been shown to have selective effects in killing or blocking the proliferation of cancer cells at concentrations which do not harm normal cells (ME Begin et al, Journal of the National Cancer Institute, 1988; 80: 188-194). Although these three are the most investigated, since the original observations, many other unsaturated fatty acids with 16 to 26 carbon atoms and two or more double bonds in either the cis or the trans configuration have been shown to have similar selective effects in inhibiting the growth of cancer cells or actually killing cancer cells at concentrations which do not harm normal cells. Such fatty acids include the essential fatty acids of the n-3 and n-6 series as shown in figure 1 and which include alpha-linolenic acid (ALA, 18:3n-3), stearidonic acid (SA, 18:4n-3), docosahexaenoic acid (DHA, 22:6n-3), arachidonic acid (AA, 20:4n-6) and adrenic acid (AdrA, 22:4n-6). Other examples of fatty acids with two or more double bonds which have similar effects include columbinic acid, parinaric acid and conjugated linoleic acid.

Figure 1



The acids, which in nature are of the all - cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids, e.g .LA as z,z-octadeca - 9,12 - dienoic acid or DHA as z,z,z,z,z,z - docosa- 4,7,10,13,16,19 - hexaenoic acid, but numerical designations based on the number of carbon atoms, the number of centres of unsaturation and the number of carbon atoms from the end of the chain to where the unsaturation begins, such as, correspondingly, 18:2 n-6 or 22:6 n-3, are convenient. Initials, e.g. EPA, and shortened forms of the name e.g. eicosapentaenoic acid, are used as trivial names in some instances.

Some of these fatty acids, notably GLA and EPA, have been tested in clinical studies in cancer patients with pancreatic cancer, other gastrointestinal cancers and breast cancer. The results have been generally favourable in terms of control of adverse effects of cancer or of its treatment, such as cachexia or radiation damage to the skin, and in terms of a modest prolongation of survival, but tumour shrinkage has not been consistently observed and, if it occurs following oral or intravenous therapy, does so in less than 10% of patients. This is true:- of the administration of GLA intravenously and orally in the case of pancreatic cancer (KCH Fearon et al, Anticancer Research 1996; 16: 867-874) where a modest prolongation of life was noted; of oral administration of combined GLA and EPA to patients with breast cancer being treated by radiation where there was a significant reduction in the skin side effects of radiation, and a modest but non-significant improvement in survival but no evidence of any tumour regression or blockade of tumour growth (AM Crellin et al, paper presented at the 28th Annual Meeting of the European Society for Radiation Research, Oxford, 24-26 September, 1997); and of oral administration of EPA to patients with pancreatic and other gastrointestinal cancers, where there was a reduction in cachexia and a favourable trend in survival but no objective evidence of tumour regression (SJ Wigmore et al, Supplement to Nutrition 1996; 12: 527-530: SJ Wigmore et al, paper presented at the meeting of the British Association of Parenteral and Enteral Nutrition, Blackpool, December 5, 1996). The only situation where tumour regression has been observed is when GLA has been directly applied to brain cancers inside the cranial cavity, thus achieving a very high local concentration (UN Das, Cancer

Letters 1995; 94: 147-155). Thus GLA, EPA and related fatty acids, when administered orally or intravenously, have useful effects as adjuncts in cancer management but do not consistently produce any evidence of tumour shrinkage.

HORMONAL MANIPULATION

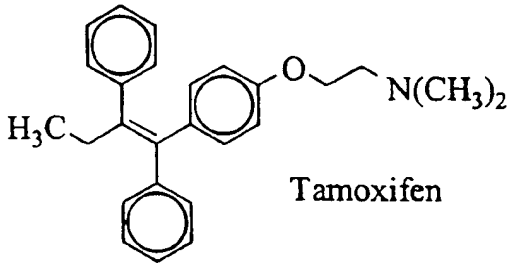
Another approach to cancer treatment, which can improve survival without necessarily leading to substantial tumour shrinkage, is that of hormonal treatment. Some cancers, notably of the breast, uterine endometrium and prostate, are frequently dependent on male or female hormones for their growth. More rarely other tumours, including those of the lung, gastrointestinal tract, liver and other organs, may occasionally show some degree of hormone dependency and hence respond to hormone manipulation. Three main types of hormone manipulation are used: removal of the endogenous hormone-secreting organs such as the ovaries, testes, adrenals or pituitary: inhibition of the synthesis of hormones, particularly of oestrogens or androgens; and antagonism of the actions of hormones by blocking binding to their receptors.

DRUGS

Drugs which inhibit hormone synthesis include gonadotrophin-releasing hormone (GnRH) and synthetic analogues of the hormone which interact with

the GnRH receptor: these block the controlling drive to the ovaries and testes. They also include inhibitors of steroid hormone synthesis such as aromatase inhibitors (e.g. aminoglutethimide, 4-hydroxyandrostenedione, plomestane, exemastane, pyridoglutethimide, fadrazole, vorazole, arimidex, CGS20267 and other drugs in development) and other steroid synthesis inhibitors which may work by various mechanisms, including cytochrome P450-dependent steroidogenesis (e.g. ketoconazole, miconazole and CGS16949A). The overall effect of these synthesis-inhibiting hormones is to reduce the production of steroids by the ovaries, testes or adrenals.

The best known drug which inhibits hormone action is the anti-estrogen, tamoxifen:-



Tamoxifen

Many other anti-oestrogens are in development, including 4-hydroxytamoxifen, toremifene, ICI-164384 and ICI-182780. Similarly there are many anti-androgens including cyproterone acetate, flutamide, nilutamide and ICI-176334. Another mechanism of anti-androgen action is to block the conversion of testosterone to dihydrotestosterone, which is the final active androgen in the prostate. This reaction is catalysed by the enzyme 5-alpha-reductase and can be blocked by finasteride and a range of similar drugs.

All hormone therapies seem to have approximately similar results in terms of response rates and there do not appear to be major differences between them (RC Stein et al, pp 629-648, in the Oxford Textbook of Oncology, Volume 1, Oxford University Press, 1995). The World Health Organisation has defined responses as follows: complete response (CR) is disappearance of all signs and symptoms of the cancer; partial response (PR) is decreasing by more than 50% of the sum of the two largest perpendicular diameters of measurable lesions; stable disease (SD) is no significant change (less than 50% shrinkage or 25% growth) of the tumour; progressive disease (PD) is growth of more than 25% in size of the tumour or the appearance of new lesions. In one substantial study of tamoxifen in breast cancer, for example, over the first three months 9% of patients showed a complete response, 21% a partial response, 20% stable disease and 50% progressive disease (A Howell et al, European Journal of Cancer and Clinical Oncology 1988; 24: 1567-72).

The patent literature includes Neuromedica WO 97/44026 and Biosignal WO 94/12530. Neuromedica concerns taxol and analogues interfering with cell division, particularly taxotere, and to combat non-solubility and non-specificity to cancer cells proposes taxotere/fatty acid conjugates, optionally used with other anticancer drugs including tamoxifen in the form of tamoxifen methionine or tamoxifen citrate. The fatty acid is present to help, for example, in the crossing of the blood brain barrier by the drug. Biosignal propose quite different

compounds, fatty-acyl derivatives of peptides, for example DHA or EPA conjugates of a somatostatin analogue or a gonadotrophin releasing hormone.

PRESENT WORK

There is nothing in the literature to suggest that there might be any strong synergistic effect between any modality of hormone therapy of cancer and any of the fatty acid treatments with GLA or EPA. However, we have completely unexpectedly found a strong and positive interaction between GLA and tamoxifen in the management of patients with breast cancer. Because all the unsaturated fatty acids appear to work by basically similar mechanisms involving lipid peroxidation, this interaction will occur between tamoxifen and other fatty acids and indeed between fatty acids and other anti-oestrogens.

In a study, 85 patients with progressive breast cancer were all treated with tamoxifen at a standard dose of 20mg per day. Of these, 47 patients received tamoxifen alone whereas 38 received tamoxifen + 2.8g per day of purified GLA. The GLA was given in the form of soft gelatin capsules, half taken in the morning and half in the evening. After 6 weeks and 3 months treatment, the status of the cancer was assessed using the WHO criteria. The results are shown in the table below. The figures show the percentages of patients in each category:

	6 WEEKS		12 WEEKS	
	T alone	T + GLA	T alone	T + GLA
Complete response	0%	0%	0%	5.3%
Partial response	8.5%	31.6%	12.8%	36.8%
Stable disease	85.1%	68.4%	80.8%	55.3%
Progressive disease	6.4%	0.0%	6.4%	2.5%

These results indicate a dramatic and wholly unexpected synergistic effect between tamoxifen and GLA. At 6 weeks the complete and partial responses to tamoxifen + GLA were 3.7 times commoner (31.6/8.5) than to tamoxifen alone and at 12 weeks the partial and complete responses to the combined treatment were 3.3 times commoner (42.1/12.8) than to tamoxifen alone. These observations were also completely different from those of the trial of GLA + EPA without tamoxifen in women undergoing radiotherapy for breast cancer (AM Crellin et al, mentioned earlier). Thus these observations represent an entirely novel and unexpected phenomenon, the enhancement of hormonal therapy of cancer by unsaturated fatty acids, in a manner which leads to actual tumour shrinkage and not just to a reduction of side effects or a prolongation of life.

THE INVENTION

The invention is as set out in the claims but in one aspect lies in the use in effective amounts, in the preparation of a medicament for the management of cancer, of tamoxifen or other anti-oestrogen together with an unsaturated fatty acid containing two or more cis or trans double bonds, the fatty acid being as such or as a bio-available derivative as discussed below. Such derivatives are present to deliver the fatty acid, and do not include derivatives of drugs, unless the anti-oestrogen itself forms such a derivative.

Alternatively, use may be made of one of said fatty acid and anti-oestrogen alone when the medicament is for co-administration with the other as a separate preparation.

Anti-oestrogens, such as tamoxifen or toremifene that are basic may be presented as salts with the fatty acids, and such salts are new and an aspect of the invention.

Further, anti-oestrogens which possess a free hydroxy group, such as 4-hydroxytamoxifen, may be presented as esters with the fatty acids. These esters may be formed directly with the fatty acid or for example with the fatty acid and the drug linked through a hydroxy/-carboxyl linker compound such as 1,3-

propane diol hemisuccinate. The latter class of compounds have been described in general in the applicant's PCT application WO 96/34846 and similar ones with certain geminal diols in PCT application WO 96/34855. Such esters are also new and an aspect of the invention.

The invention extends further to medicaments as such, containing the fatty acid and anti-oestrogen as such or as derivatives particularly the new salts or derivatives above, and to therapy lying in the cancer management itself. Management is not only in particular in respect of the reduction of tumour size, as shown in the study reported above, but also in prophylaxis. The synergy is to be expected in preventive mode as much as in overt disease as this is essentially early treatment of cancerous or pre-cancerous cells before any development of tumours has taken place.

Especially use is made of tamoxifen with GLA or DGLA, and especially the cancer is breast cancer.

The fatty acid, suitably C_{16} to C_{26}, may in particular be an n-6 or n-3 essential fatty past the delta-6 desaturation step, particularly GLA, DGLA, SA, EPA or DHA, or it may be columbinic acid, parinaric acid or conjugated linoleic acid.

Conveniently the medicament is in single or divided dosage form suited to administration of daily amounts of the anti- oestrogen conventional for its use

in the absence of fatty acid and 0.1 to 20g preferably 0.2. to 10g very preferably 0.5 to 5g of the fatty acid daily.

The fatty acids may be provided orally or parenterally in any bio-available form including the free acid, salts such as lithium, sodium, potassium, zinc or any other salt; mono-, di- or triglycerides; ethyl or other esters suitably C_1 to C_6 alkyl; cholesterol esters; phospholipids; amides suitably C_1 to C_6 alkyl; or any other pharmacologically acceptable derivatives delivering the acid in the required amount including the diol derivatives of the applicant's PCT WO 96/34846 and PCT WO 96/34855. Such derivatives are of materials not acting as drugs in themselves, unless possibly of the anti-oestrogen forming the other component of the composition, where so derivatisable. Bioavailability may for example be shown by the derivatives giving the effects of the fatty acids or their natural glyceride esters, or by direct analysis of fatty acid concentrations in blood plasma or other tissues by standard techniques for example those of Pelick et al p.23 "Analysis of Lipids and Lipoproteins" Ed. Perkins, Am. Oil Chemists Soc., Champaign, Illinois, USA.

SYNTHESIS EXAMPLES

A. *Salt of tamoxifen with GLA*

(Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanammonium octadeca-6Z,9Z,12Z-trienoate

A mixture of tamoxifen (200mg, 0.54mmol) and octadeca-6Z, 9Z, 12Z-trienoic acid (140mg, 0.5mmol) in methanol (5mL) was swirled gently at room temperature for a few minutes until a clear pale yellow solution resulted. An aliquot of this solution (0.2mL) when added to water (0.8mL) yielded a milky suspension. The remainder of the methanolic solution was concentrated to dryness to yield (Z)-2[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanammonium octadeca-6Z,9Z,12Z-trienoate as an oily residue. This residue was soluble in hexane.

B. *Ester of EPA with 4-hydroxy-tamoxifen*

(E)-1[4'-(2-dimethylaminoethoxy)phenyl]-1-[4-(eicosa-4Z,7Z,10Z,13Z,16Z-pentaenoyloxy) phenyl]-2-phenylbut-1-ene

A stock solution of eicosa-4Z,7Z,10Z,13Z,16Z-pentaenoic acid (195mg. 0.65mmol)in dichloromethane (2.5mL) was prepared. A second stock solution of 1,3-dicyclohexylcarbodiimide (150mg, 0.72mmol) and 4-(N,N-dimethylamino)pyridine (90mg, 0.72mmol) in dichloromethane (2.5mL) was also prepared. An aliquot (0.25mL) of each of these solutions was added to 4-hydroxytamoxifen (25mg. 0.065mmol) and the mixture was gently shaken until a clear solution resulted. The headspace was gently purged with nitrogen and the mixture was allowed to stand overnight at room temperature. After this time a precipitate of 1,3-dicyclohexylurea was apparent. Tlc analysis (tert butyl methyl ether + trace triethylamine) indicated clean formation of a new product

(E)-1-[4'-(2-dimethylaminoethoxy)phenyl]-1-[4-eicosa-4Z,7Z,10Z,13Z,16Z-pentaenoyloxy) phenyl]-2-phenylbut-1-ene which stained both under UV illumination and with ceric ammonium molybdate staining.

USE EXAMPLES

1. 20mg/day of tamoxifen citrate, (Z) 2-[4-(1,2-diphenyl-1-butenyl phenoxy]-N,N-dimethylethanamine 2-hydroxy-1,2,3 propane tricarboxylate (1:1), or other amount of 10 to 60 mg/day conventional in itself, as an anti-oestrogen in tablet form to be co-administered with 4g/day of GLA as the free acid, lithium salt, ethyl ester, triglyceride, phospholipid, 1,3- propane diol diester, or other derivative in hard or soft gelatin capsules each containing 0.5 or 1g of GLA, in the management of breast or other cancer.

2. As 1 in which the anti-oestrogen is a 60mg tablet of toremifene instead of the tamoxifen or other conventional amount of 30 to 240 mg daily.

3. 20 mg/day of tamoxifen as such or as the GLA salt, incorporated in 5mg amounts in four 0.5g GLA- content capsules to be administered as in 1.

4. 20mg/day of 4-hydroxy tamoxifen gammalinolenate ester incorporated in capsules and administered as in 3.

5-8 As in 1 to 4 in which the fatty acid is one of DGLA, SA, EPA, DHA, or other n-6 or n-3 essential fatty acid past the delta-6 desaturation step, or columbinic acid, parinaric acid or conjugated linoleic acid, instead of GLA, in corresponding molar amount.

CLAIMS

1. The use, in the preparation of a medicament for the management of cancer and especially reduction of tumour size, of tamoxifen or other anti-oestrogen together with an unsaturated fatty acid containing two or more cis or trans double bonds, the fatty acid being as such or as a bioavailable derivative (but not a derivative of a drug unless the anti-oestrogen itself), or such use of one of said fatty acid and anti-oestrogen when the medicament so prepared is for co-administration with the other.

2. As claim 1, wherein the medicament is in single or divided dosage form suited to administration of daily amounts of the anti- oestrogen effective for its use in the absence of the fatty acid.

3. As claim 1, wherein the medicament is in single or divided dosage form suited to administration of 0.1 to 20g preferably 0.2 to 10g very preferably 0.5 to 5g of the fatty acid daily.

4. As claim 1, 2 or 3, wherein the fatty acid is an n-6 or n-3 essential fatty acid past the delta-6-desaturation step particularly GLA, DGLA, SA, EPA or DHA, or is columbinic acid, parinaric acid or conjugated linoleic acid.

5. As claim 1, 2 or 3, wherein the fatty acid is GLA or DGLA specifically.

6. As any of claims 1 to 5, wherein the anti-oestrogen is tamoxifen, particularly in an amount of 10 to 60 mg daily.

7. As any of claims 1 to 5 , wherein the anti-oestrogen is toremifene (particularly in an amount of 30 to 240 mg daily), 4-hydroxytamoxifen (particularly in an amount of 10 to 60 mg daily), ICI-164384, or ICI 182780.

8. As any of claims 1 to 7, wherein the cancer is breast cancer.

9. A medicament for the management of cancer and especially the reduction of tumour size, containing both a fatty acid and an anti-oestrogen as set out in any preceding claim.

10. Management of breast or other cancer by use of a medicament prepared or characterised as in any preceding claim.

11. A salt of a fatty acid (as set out in claim 1, 5 or 6), and tamoxifen or other anti-oestrogen with a basic centre.

12. An ester of a fatty acid (as set out in claim 1, 5 or 6), of 4-hydroxy tamoxifen or other anti-oestrogen with a hydroxy group, esterification being direct or through a 1,3-propane diol hemi-succinate or other hydroxy/carboxyl linking compound.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 99/00563

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 44026 A (NEUROMEDICA, INC., USA) 27 November 1997 (1997-11-27) cited in the application page 19, line 11; claim 14 page 21, line 20-25 page 22, line 4	1-12
Y	HORROBIN D F: "NUTRITIONAL AND MEDICAL IMPORTANCE OF GAMMA-LINOLENIC ACID" PROGRESS IN LIPID RESEARCH, vol. 31, no. 2, 1 January 1992 (1992-01-01), pages 163-194, XP000196482 ISSN: 0163-7827 page 185, paragraphs 3,4	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/GB 99/00563

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 34855 A (SCOTIA HOLDINGS PLC ;MANKU MEHAR (GB); PITT ANDREA (GB); KNOWLES P) 7 November 1996 (1996-11-07) abstract; claim 12	1-12
Y	WO 94 12530 A (BIOSIGNAL KUTATO FEJLESZTOE ;SYNTHETIC PEPTIDES INC (CA)) 9 June 1994 (1994-06-09) page 25, line 31 - page 26, line 5; claims 1-3	1-12
X	EP 0 707 850 A (SCOTIA HOLDINGS PLC) 24 April 1996 (1996-04-24) column 2, line 30-45	1-12
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US KENNY, F. S. (1) ET AL: "Gamma linolenic acid with tamoxifen as primary therapy in breast cancer." retrieved from STN XP002108763 abstract & BRITISH JOURNAL OF CANCER, (1998) VOL. 78, NO. SUPPL. 2, PP. 45. MEETING INFO.: JOINT MEETING OF THE BRITISH ONCOLOGICAL ASSOCIATION, THE ASSOCIATION OF CANCER PHYSICIANS AND THE ROYAL COLLEGE OF RADIOLOGISTS NOTTINGHAM, ENGLAND, UK JULY 5-7, 1998 AS,	1-12
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US DE ANTUENO, R. ET AL: "Effect of polyunsaturated fatty acid propane diol esters on mice treated with tamoxifen." retrieved from STN XP002108764 abstract & PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, (MARCH, 1999) VOL. 40, PP. 361. MEETING INFO.: 90TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH PHILADELPHIA, PENNSYLVANIA, USA APRIL 10-14, 1999 AMERICAN ,	1-12

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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